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Per- and polyfluorinated substances (PFASs): Environmental challenges

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ABSTRACT

Long-chain perfluoroalkylated acids are persistent in the environment, leading to ubiquitous exposure of biota. They have been listed as very persistent, very bioaccumulative and toxic by Public Health Authorities. Their production and use have been regulated in most western countries but their production has increased in other geographical area. Animal studies show highly diverse and complex, product-, species- and gender-dependent pharmacodynamics and toxicity profiles. Human epidemiologic studies unveiled liver, developmental and other adverse health effects, while further effects remain inconclusive. Alternative short-chain products are technically much less performing. Alternative long-chain processing aids have not been proven environmentally advantageous. Risk assessment is difficult and highly uncertain. Little breakthrough products or technologies have yet emerged that can match the feats of fluorinated surfactants and fluorinated polymers. Radical, disruptive new solutions are needed. Meanwhile, more reasonable, more selective use of these compounds appears indispensable in order to reduce exposure while preserving their societal benefits and without penalizing developing countries. Progress in the risk management of per- and polyfluorinated substances is, however, impeded by considerable knowledge and information gaps, and will demand sustained multidisciplinary efforts.

1. Introduction: unrestricted use of PFASs is not sustainable

Investigation of the environmental and health effects of per- and polyfluoroalkylated substances (PFASs[1]) has developed into a sizable, hot and complex scientific field with a current output exceeding 400 papers per year [1••]. The present review attempts to excerpt from this recent and profuse literature some salient points and balanced critical opinions destined for physicochemists attentive to environmental issues. A companion paper recapitulates the production routes and (so far) unmatchable basic properties of PFASs that led to their countless industrial, technical and consumer uses [2••].

Unrestricted use of the "historical" PFASs is definitely not sustainable due to environmental persistence, bioaccumulation and probable health effects. When it was realized that bioaccumulation and likely also health risks decrease with decreasing *F*-chain[2] length, PFASs were formally divided into long- and short-*F*-chain compounds. The former refers to *F*-alkylcarboxylic acids (PFCAs) with 7 and more fluorinated carbons (e.g. PFOA, PFNA; Table 1) and *F*-alkane sulfonates (PFSAs) with 6 and more fluorinated carbons (e.g. PFHxS, PFOS), and substances that have the potential to degrade to long-chain *F*-alkyl acids (PFAAs) [3••].

2. Long-*F*-chain PFASs are persistent, and now ubiquitous

The environmental persistence, ubiquity and bioaccumulation of long-*F*-chain PFASs have been definitively confirmed. Their persistence reflects one of the major assets of PFAAs, their outstanding thermal stability and chemical inertness. The sources of PFAS emissions to the environment, both direct (from manufacture, use and disposal of products that contain *F*-compounds as ingredients, residues of reactants, processing agents and undesired impurities) and indirect (from degradation of PFAA precursors present in industrial and consumer products) continue to be identified [1••, 4••]. Ocean water is the main global reservoir of PFAAs [5•–9•]. A recent comprehensive quantitative inventory of global production and emissions of C_4–C_{14} PFCAs over the 1951–2030 period has been produced [4••]. A companion paper discusses sources that are known to exist but cannot be quantified presently for lack of information [10]. The total emissions (1951 to 2015) of PFCAs (mostly PFOA and PFNA-based products) were estimated to be 2610 to 21,400 tons [4••]. Projected emissions between 2015 and 2030 (mainly from PFOA

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[1] The terminology and acronyms are those defined by Buck et al. [1], used in [2] and exemplified in Table 1; further abbreviations are spelled out in the caption of Fig. 1.

[2] The customary italic notation *F*- will be used for "perfluoro". By extension, *F*-chain means perfluoroalkyl chain, *F*-polymer means perfluoroalkylated polymer, etc.

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Table 1
Typical environmentally relevant PFASs discussed in this paper and their acronyms.

Class	Generic formula	Acronyms, examples
F-alkyl carboxylic acids	$C_nF_{2n+1}COOH$	PFCAs, n = 3: PFBA; 4: PFPeA; 5: PFHxA; 7: PFOA; 8: PFNA
PFOA ammonium salt	$NH_4^+C_8F_{17}COO^-$	APFO
F-alkane sulfonic fluorides	$C_nF_{2n+1}SO_2F$	n = 6: PHxSF; n = 8: POSF
F-alkane sulfonic acids	$C_nF_{2n+1}SO_3H$	PFSAs, 4: PFBS; 6: PFHxS; 8: PFOS
F-octane sulfonamide	$C_8F_{17}SO_2NH_2$	FOSA
N-alkyl *F*-octane sulfonamidoethanols	$C_8F_{17}SO_2NRCH_2CH_2OH$	*N*-MeFOSE, *N*-EtFOSE
N-methyl *F*-butane sulfonamidoethanol	$C_4F_9SO_2N(CH_3)CH_2CH_2OH$	*N*-MeFBSE
F-telomer sulfonate (K^+ salt)	$K^+\ C_6F_{13}CH_2CH_2SO_3^-$	6:2 FTSA (K^+)
F-telomer alcohols	$C_nF_{2n+1}C_2H_4OH$	*n*:2 FTOHs
Secondary *F*-telomer alcohol	$C_7F_{15}CH(CH_3)OH$	7:2 sFTOH
F-telomer acids	$C_nF_{2n+1}CH_2CH_2COOH$	*n*:3 FTCA
Unsaturated *F*-telomer acids	$C_nF_{2n+1}CH{=}CHCOOH$	*n*:3 FTUCA
F-telomer monophosphates	$C_nF_{2n+1}C_2H_4OP(O)(OH)_2$	*n*:2 monoPAPs
F-telomer diphosphates	$(C_nF_{2n+1}C_2H_4O)_2P(O)OH$	*n*:2 diPAPs
F-alkylphosphonic acids	$C_nF_{2n+1}P(O)(OH)_2$	PFPAs
F-alkylphosphinic acids	$(C_nF_{2n+1})(C_{n'}F_{2n'+1})P(O)OH$	PFPiAs
N-ethyl *F*-octane sulfonamido ethanol phosphate diester	$[C_8F_{17}SO_2N(Et)CH_2CH_2O]_2P(O)OH$	SAmPAP diester
F-telomer acrylate monomer	$C_nF_{2n+1}C_2H_4OC(O)CH{=}CH_2$	*n*:2 FTAc
F-telomer metacrylate	$C_nF_{2n+1}C_2H_4OC(O)C(CH_3){=}CH_2$	*n*:2 FTMac
Polyfluoroalkyl ether acid	$NH_4^+\ CF_3OC_3F_6OCHFCF_2COO^-$	ADONA
Polyfluoroalkyl ether acid	$C_3F_7OCF(CF_3)COO^-$	GenX
Polyfluoroalkyl ether acid	$ClC_6F_{12}OC_2F_4SO_3^-$	F-53B
(*F*-alkyl)alkyl diblocks	$C_nF_{2n+1}C_mH_{2m+1}$	SFAs, *FnHm* diblocks

For a more complete set of formula see [1] or [2].

use in China and Russia, and from degradation of long-*F*-chain *F*-telomer alcohols (FTOH)-based products) are from 20 to 6420 tons.

FTOHs (primarily 8:2 FTOH) and FOSEs (primarily *N*-MeFOSE) and their derivatives are found in high levels near carpet production and treatment facilities, and in consumer goods [11]. Elevated PFAS levels are found in the vicinity of airports and fire-fighting training centers [12–15]. Accidental spills have released considerable amounts of PFASs to ground and surface waters [16]. Many *F*-surfactants (C_4 to C_{12}) are present in aqueous film forming fire-fighting foams [17]. No less than 103 PFASs (*F*-chains from C_3 to C_{15}) were detected in 10 fire-fighting products [18]. Many of them were measured in above average amounts in the blood of fire fighters [19], including PFOS and PFHxS [20]. Polymer degradation may be a significant source of PFCAs [21]. Discharges from wastewater treatment plants (WWTPs), *F*-chemical production sites and landfills, amendment of soil with industrially impacted biosolids from WWTPs and urban runoff waters [22–29] also participate to dissemination of and exposure to PFASs. Minor amounts of short-*F*-chain PFASs arise from direct surface fluorination of polymer goods when traces of oxygen are present [30].

PFASs adsorb strongly onto suspended solid particulates and sediments, especially the longer-*F*-chain (C_{12}–C_{15}) PFCAs [31]. PFOA was shown to interact with soil-bound proteins [32]. Adsorption to soil, sediments and sewage sludge, an important determinant of subsequent PFAS release to surface and ground waters and into crops, may have been underestimated [29]. Interestingly and unexplained, PFCAs and *N*-MeFOSE, and PFSAs adsorb differentially on smaller and larger particles, respectively [33]. PFOS may form complexes with clay through hydrogen bonds at the mineral's surface, while PFHxS would bind with the inner OHs [34].

The ubiquitous presence of long-*F*-chain PFASs continues to be documented [1••, 5•, 7, 8, 22, 29, 35–44••], including in food and drinking water [14, 24–26••, 35, 39•, 45–48], dust [49–51], wildlife [37•, 52•–57] and humans [40, 58••–78•].

Environmental PFAS distribution is not uniform (Fig. 1). While open ocean water PFOA levels are typically in the 10–80 pg/L range (1–20 pg/L for PFOS) [5•], these levels can be several orders of magnitude higher in industrialized areas [79], coastal waters [5•, 41], or downstream from an airport [13]. Drinking water PFAS levels are usually low and considered safe. Fresh water PFAA concentrations can, however, be higher near a direct industrial source [25] or near a fire-fighting training area [16, 80]. Important accidental local drinking water contaminations have occurred [80, 81].

Numerous phosphorus compounds [64], including *F*-alkylated phosphate monoesters (*n*:2 monoPAPs) and diesters (*n*:2 diPAPs) [27, 72, 82, 83], *F*-alkylphosphonic acids (PFPAs) [84•], *F*-alkylphosphinic acids (PFPiAs) and *F*-octane sulfonamidoethanol phosphate diester (SAmPAPs) [64] are now found in surface waters, WWTP sludge and effluents, sediments and human sera. Their degradation contributes to exposure to PFAAs [27, 84•, 85].

3. Atmospheric and biological degradation of *F*-surfactants and *F*-polymers yield PFAAs

3.1. Atmospheric transport and reactions

Long-range dissemination involves both an aquatic (oceanic) route that is favored for the more water soluble compounds (e.g. *F*-acids and their salts), and an atmospheric route for the more volatile, neutral ones (e.g. *F*-telomer alcohols (*n*:2 FTOH), sulfonamidoethanols (FOSEs), phosphate diesters (diPAPs)) [6, 36••, 113]. The latter have atmospheric life-times of tens of days and are eventually degraded to PFAAs that can then be deposited in remote places. The anionic species are preferentially transported in solution by oceanic water currents, in surface foam and aerosols. A recent estimation suggested pK_a values of 0.5 for PFOA and below 0.3 for PFASs [114]. The relative contributions of the two routes are still being debated [6, 36••, 113]. Polar ice melting consecutive to global warming may allow release of atmospherically deposited PFOA to the oceans [9•].

The atmospheric chemistry, degradation pathways and lifetime of PFAA precursors, the generation of PFCAs from precursors, their sources and levels have been thoroughly analyzed [36••]. PFAAs (e.g. PFOA, PFNA, PFOS, PFBS) are extremely refractory to degradation and there is still little definite evidence for their degradation in environmentally relevant conditions. Direct photolysis of PFOA is, for example, barred since it does not absorb light from the solar spectrum. Indirect degradation by hydroxyl radicals produced in the presence of natural sensitizers (e.g. nitrate and ferric ions and seawater) was not detected when PFOA was irradiated in the 290–800 nm range [115]. PFOA was, however, degraded (98% in 28 days) in the presence of Fe(III) under sunlight [116]. Radical reactions involving UV-induced electron transfer from PFOA to Fe(III) or attack by hydroxyl radicals were proposed. A paper suggesting that photolysis of long-*F*-chain PFAAs was possible in environmental conditions, and that the shorter *F*-chain homologues were more resistant to photodegradation [117], has been severely criticized [118]. Interestingly, PFOA has been successfully degraded to shorter PFCAs and F^- using a horseradish peroxidase (an iron(III) heme-centered enzyme)-catalyzed reaction with hydrogen peroxide and a co-substrate, 4-methoxyphenol, a reaction that may have potential for the treatment of PFCA-contaminated waters [119]. Atmospheric degradation of *n*:2 FTOH-derived surfactants and polymers in atmosphere-mimicking conditions has been intensely studied [36••]. An "unzipping" cycle that

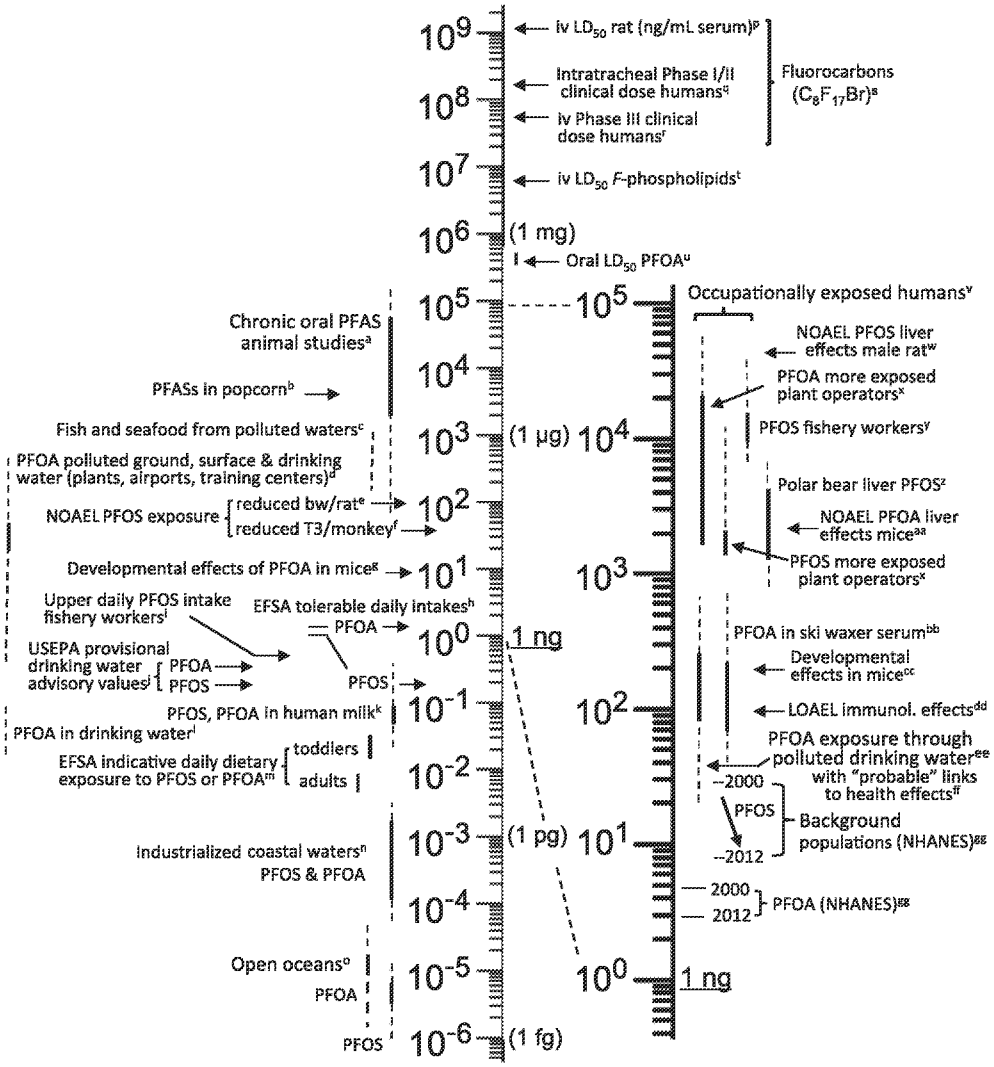

Fig. 1. Typical environmental exposures to and intakes of long-*F*-chain PFASs (PFOA and PFOS), along with some median lethal doses (LD_{50}), no-observed-adverse-effect-levels (NOAELs), lowest-observed-adverse-effect-levels (LOAELs), tolerable daily intakes (TDIs) and related data; logarithmic scales; data expressed as ng/g body weight (bw) or ng/mL (blood serum, milk, water) and ng/g_{bw}/day, unless indicated otherwise. a: ng/g_{bw}/day; b: up to 3 g/kg [86]; c: ng/g wet weight [13, 35, 87]; d: [5, 16, 88••]; e: [89••]; f: reduced triiodothyronine (T3) level [89••]; g: PFOA gavage, ng/kg_{bw}/day [26••, 90, 91]; h: (TDIs, ng/g_{bw}/day) [45]; i: [87]; j: [92]; k: ng/mL [93–95]; l: [14, 47]; m: [96]; n: [5, 41]; o: [5]; p: 40 g/kg_{bw} intravenous (iv) emulsion [97], i.e. ~1.2×10^9 ng/mL serum (~65 mL blood/kg_{bw}, Hct ~50%); q: liquid ventilation ~200 mL/kg_{bw} over ~80 h [98]; r: 2.7 g $C_8F_{17}Br/kg_{bw}$ emulsion iv [97], or ~70×10^6 ng/mL serum (70 kg patient, 5 L blood, hematocrit 45%); s: *F*-octyl bromide, produced by telomerization, 99.9% pure; t: 7.7 g/kg_{bw}, mice [99]; u: rodents [100]; v: ng/mL blood serum; w: [101]; x: [76••, 102]; y: [87]; z: ng/g liver [52•, 53]; aa: serum level gavage [91]; bb: [103, 104]; cc: serum level in pups [91]; dd: oral PFOS in a strain of mice [105]; ee: in serum [106–108]; ff: the C8 Health Project [108–111]; gg: [112]. Data expressed in different units are not directly comparable.

involves *F*-alkoxy, *F*-alkyl and *F*-alkyl peroxy radicals, and splitting off of COF_2 yields shorter *F*-chain PFCA homologues.

3.2. Biodegradation

No definite evidence of biodegradation of PFAAs has yet been produced.

Biodegradation of long-chain *F*-telomer alcohol and *F*-alkane sulfonamide derivatives and precursors by various bacteria and by microorganisms present in activated sludge, soil and sediments, as well as by hepatocytes and microsomes in vitro, and in animals, has been confirmed [84•, 120–124•] [125–127••]. FTOHs play a pivotal role in the degradation processes of many commercial products (e.g. esters, PAPs, acrylate, metacrylate monomers and polymers), which first hydrolyze to FTOHs. Outcome, rates and yields of aerobic microbial degradation of *n*:2 FTOHs depend critically on *F*-chain length, isomer, bacterial strain, environmental matrix (type and origin of soil, sediment, WWTP sludge, etc.), co-metabolites and testing conditions, reflecting, among others, differences in microbial and fungal populations and enzyme efficacy and specificity [126, 128–130]. *n*:2 FTOHs ($n = 4, 6, 8$) were biodegraded by *Pseudomonas* bacterial strains, leading to removal of CF_2 units and production of short-*F*-chain acids [120]. Aerobic biodegradation in soil of 8:2 FTOH stearate ester and citrate triester surfactants has been established [131]. *F*-telomer ethoxylates ($C_nF_{2n+1}(CH_2CH_2O)_pH$, $n = 6–10$, $p = 0–13$) were aerobically degraded in WWTP effluent. Biodegradation of *N*-EtFOSE in marine sediments was much slower than in sludge, while SAmPAP diester proved rather resistant [132]. *F*-telomer sulfonate 6:2 FTSA (K^+ salt) was slowly biotransformed by activated sludge [133]. The identified "one-carbon removal pathway" for sequential removal of CF_2 groups in sludge allows aerobic conversion of 5:3 FTCA to 4:3 FTCA, and then to 3:3 FTCA, along with PFPeA and some PFBA [121]. 6:2 mono- and diPAPs, and mixtures of *n*:2 monoPAPs ($n = 4, 6, 8, 10$) were microbially hydrolyzed to FTOHs, eventually releasing PFCAs in WWTP effluents [27, 82, 84•, 85]. Microbial degradation of 8:2 FTAc and 8:2 FTMac monomers in aerobic soil yielded first 8:2 FTOH and then 7:2 sFTOH, FTCAs and PFCAs, including PFOA [134].

Surprisingly little is published about the environmental biodegradation and fate of the commercially important, large tonnage *F*-polymers. Conflicting studies concluded that biodegradation of a commercial

acrylate-linked copolymer with FTOH side-chains did occur in soil and could be a significant source of PFCAs to the environment [21] or, on the contrary, contributed little to PFOA pollution [135]. Higher levels of PFOA, PFNA, PFDA and PFOS have often been found in WWTP outflows relative to inflows, also indicating biotransformation of precursors, as well as ineffective removal of PFASs by conventional wastewater treatment [22, 88••, 136]. Microbial intervention is also likely involved in the quasi-irreversible binding of PFASs to soil [123, 137].

4. No one escapes exposure, but some are more exposed than others, or more vulnerable

The presence of PFASs in biota is ubiquitous but not uniform. It increases with trophic levels, maximizing for the predators sitting at the top of the food chains, to which we belong. However, exposure and the associated risk are clearly not the same for the general (background) population and for those more exposed, which includes workers producing or using PFASs and populations living near a source of contamination. Serum levels can be several orders of magnitude higher in occupationally exposed than in background populations (Fig. 1).

4.1. PFASs bioconcentrate, bioaccumulate and biomagnify

Bioconcentration (direct uptake of chemical from its environment) and bioaccumulation (uptake from all exposures, including food) of PFASs in animals increase steeply with *F*-chain length [41, 110, 138–140•] [141–142]. For a given *F*-chain length, bioaccumulation is more effective for PFSAs than for PFCAs (e.g. PFOS > PFNA), possibly because of tighter binding to proteins [143]. Bioaccumulation depends also on species, with PFBS and PFOS mainly found in crabs, PFOS and PFDA in fish, and PFHxS in gastropods and bivalves [41]. Upper limits have been set for bioconcentration factors for PFASs to be considered as non-bioaccumulative [138]. Biomagnification of PFASs (increased pollutant concentration in predator vs. prey) is observed when moving up within food chains and trophic levels, and is particularly effective for PFOS and the longer-*F*-chain PFCAs [37•, 52•, 144], in top predators such as bear [52•] or wild mink [55]. Trophic magnification has been illustrated by studies of PFOS and C_8–C_{12} PFCAs in the lichen–caribou–wolf food chain [145], or plankton–fish–egret chain in eutrophic freshwater [142]. Very long, up to C_{15} PFCAs were detected in fish [56] and eggs of sea birds [54]. Transfer of PFOS from zebra fish to their eggs has been established [146]. The distribution and monitoring of PFAAs in wildlife has recently been reviewed [57].

4.2. Human exposure

Worldwide human exposure to PFASs has been confirmed [3, 40, 58••, 66••, 70, 78•, 147, 148]. For the general population the major source of contamination arises from food and sometimes drinking water (>90%) [35, 58••, 61, 70, 71, 148–153]. PFOS is generally the most abundant PFAS found in humans, the second usually being PFOA, and PFHxS the third [70]. Exposure to PFOS and the higher PFCAs ($n \geq 9$) through consumption of fish, in particular from polluted waters, can be very large [58••, 87, 148, 149, 154]. PFASs migrate easily and in substantial amounts from food packaging into food [83, 86, 155]. PFAA levels in drinking water are usually low, unless near a point source of PFASs. PFOA serum levels can then increase significantly with on-going drinking water exposure [26••]. Cows, and hence, dairy milk are not sheltered against PFAS pollution [156, 157].

Human exposure also arises from indoor and ambient air and house dust. Outdoor air carries volatile FTOHs, FOSAs, FOSEs, etc. typically in the 10–100 pg/m^3 range, with higher concentrations in urban versus rural sites and near specific point sources [58••]. Non-volatile PFASs, in particular PFOA, are adsorbed on airborne particles [33]. Concentrations of volatile PFASs (mainly 8:2 FTOH, followed by *N*-MeFOSE) in indoor air in homes, classrooms and offices can be several orders of magnitude larger than in outdoor air [51, 60, 158]. House dust (mainly from impregnation sprays and impregnated carpets) can be a significant contributor to exposure to the less volatile PFAAs [49–51, 58••, 60, 159–162]. Up to 27 different PFASs were detected in a study of house dust [163•]. FTOH precursors, including PAPs, appear to be significant sources of human PFCA contamination [85]. Lesser exposure sources include contact with impregnated clothes, footwear, upholstery, and other goods that have been treated with PFASs or contain unintended residues used during manufacturing.

Average background PFAS levels appear to be on the same order of magnitude worldwide, but with substantial local variations. An assessment of North American and European long-term consumer exposure estimated daily uptakes in the range of 3 to 220 ng/kg$_{bw}$ for PFOS and 1 to 130 ng/kg$_{bw}$ for PFOA under various scenarios [164]. An "intermediate" scenario estimate was 12–15 ng/kg$_{bw}$/day for PFOS for adults (up to 55 ng/kg$_{bw}$/day for infants) and 2.5–3 ng/kg$_{bw}$/day for PFOA (adults; up to 10 ng/kg$_{bw}$/day for infants). Another exposure assessment for the general adult population in western countries estimated average (and upper) overall exposure (ng/kg$_{bw}$/day) to 1.6 (8.8) for PFOS, 2.9 (12.6) for PFOA, 1.6 (11) for FOSA/FOSEs, and 0.14 (1.1) for FTOHs [58••]. Other studies on human exposure include [60, 67, 150].

An advanced estimation (2012) of dietary exposure was ~5–10 ng/kg$_{bw}$/day for PFOS, 4–7 ng/kg$_{bw}$/day for PFOA, the most important contributors being fish and seafood, fruit and fruit products [96]. Exposure of toddlers was 2–3 times higher than for adults. The report concluded that human dietary exposure to PFOS and PFOA is highly unlikely to exceed health-based guidance values.

Recent US National Health and Nutrition Examination Survey (NHANES) data (2011–2012) for the general population give mean serum concentrations (ng/mL) of ~5 (PFOS), ~2 (PFOA), ~1.3 (PFHxS) and ~0.9 (PFNA) [112]. Data from the 1999 to 2008 period were 14–30 (PFOS), 4–5 (PFOA), ~2 (PFHxS) and 0.5–1.5 (PFNA) ng/mL (Fig. 2; see discussion of trends in Section 12) [63••]. In 2010, US Red Cross Blood Donors plasma levels (ng/mL) were 8.3 (PFOS), 2.4 (PFOA), 1.3 (PFHxS) and ~0.8 (PFNA) [66••]. The very persistent higher PFCAs are also commonly found in human sera [61, 165]. C_7–C_{11} and

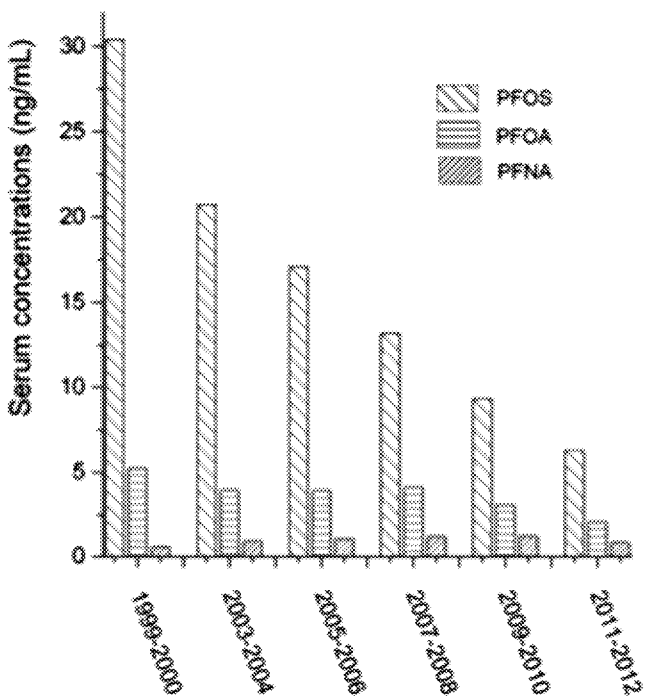

Fig. 2. Geometric mean concentrations (ng/mL) of PFOS, PFOA and PFNA in human serum over the years.
From NHANES data [112].

C_{13} PFCAs and 4:2 to 8:2 diPAPs were found in most inhabitants of two German cities [72], as well as C_4–C_{10} PFASs and a wide range of their precursors [73]. Increasing concentrations of PFNA likely indicates indirect exposure via biotransformation of FTOH-based substances [151•].

Substantial sex differences have been observed. Women have age-dependent lower PFOS, PFOA and PFHxS levels than men [63••], due in part to elimination by menstruation [166, 167]. Human serum levels of *n*:2 diPAPs (mainly from food packaging [83]) were ~4.5 ng/mL [82]. Information on human exposure to PFAS in developing countries is generally still scarce. PFOS and PFHxS levels in Chinese cities have become significant [168, 169].

Biomonitoring of identified higher exposed populations has recently been reviewed in details [76••]. Occupational exposure of fluorochemical plant workers can be 2–3 orders of magnitude larger than for the general population (Fig. 1). Typical mean occupational PFOS and PFOA serum concentrations are in the 300–900 ng/mL range, but can be 2–10 times higher in specific more exposed job groups (the highest ever reported were 114,000 ng/mL for PFOA and 12,800 ng/mL for PFOS) [76••]. The serum of ski waxing technicians had 10–40 times higher blood concentrations of very long-*F*-chain PFASs than the general population [103, 104, 170]. Employees of fisheries located near fluorochemical producer and user plants in China experienced huge PFSA serum levels (median PFOS and PFHxS concentration of 10,400 ng/mL; 3540 ng/mL for family members, as compared to ~20 ng/mL for a reference group) [87]. Fire fighters constitute another occupationally exposed population [19].

More exposed resident populations are those living near a point source of PFASs, as through polluted drinking water (Fig. 1). In one instance of contamination from spreading of polluted waste material on agricultural land, the exposed children and adults had 4 to 8-fold larger PFOA blood plasma levels (25–29 ng/mL) than controls (3–6 ng/mL) [154]. Populations near an *F*-polymer production plant had PFOA blood serum levels (mean of 427 ng/mL for residents who worked at the plant and drank the local water) 60 to 75 times larger than those of the general US population that were traced to residential drinking water [171]. PFOA levels varied with distance of residence to chemical plant and employment at the plant. PFOS and PFOA contamination of surface water, rivers and drinking water have become serious in certain areas and cities in China [168, 169].

Children, especially toddlers, are more exposed than adults on a body weight basis, due to higher relative food consumption and to hand-to-mouth transfer from impregnated carpets and ingestion of dust, resulting in higher PFAS serum levels than for adults [35, 49, 51, 150, 158, 159, 164, 172, 173].

In utero and postnatal exposures are of particular concern. PFAAs cross the placental barrier, exposing neonates via their mother's blood [26••, 174–184]. PFOS and PFCAs are generally in lower concentrations in cord serum than in maternal serum [174]. Transfer of PFOA from mother to fetus has also been inferred from consistently lower PFOA serum levels in pregnant versus non-pregnant women [185]. Placental transfer involves some selectivity, leading, for example, to higher PFOA and lower linear PFOS levels in cord versus maternal blood plasma [181]. Even the very long *F*-chain PFUnA was found in cord serum [179].

Numerous PFASs have been detected in breast milk, though in concentrations much lower than in the mother's blood plasma [58••, 67, 77, 93, 178, 186–191]. Lactational transfer (and baby formulations [94]) can nevertheless be the primary source of exposure to PFASs, mainly PFOS, for infants [60]. Accumulation through breast-feeding can, after six months, lead to body burdens similar to (PFOS) or higher than (PFOA) those seen in adults [58••]. PFOA and PFOS blood levels were seen to decrease markedly in mother while it increased in child during breast feeding [191]. Longer breast-feeding led to higher serum PFAA levels in young girls [77]. PFOS intakes from breast milk may in certain area exceed the provisional tolerable daily intakes (pTDIs) for the most exposed children [94].

5. Animal (including human) data show widely different pharmacokinetics, including elimination rates

Pharmacokinetics and (eco)toxicological investigation results are characterized by wide product, species, gender and other variations that are far from being fully understood. Oral PFAS *absorption* is generally rapid. *Distribution* occurs primarily in the liver, plasma and kidney, but depends somewhat on compound, animal and type of exposure [192]. The liver, lung and kidney are major target organs for PFAAs. In the blood, PFAAs bind to plasma proteins, primary albumin [193–195]. Two distinct binding sites were identified by NMR in human albumin for PFOA and PFHxA [193]. Both acids readily displace endogenous oleic acid from its usual binding site, raising questions about possible interferences with the pharmacokinetics of fatty acids and drugs. Both acids changed the secondary structure of the protein, PFOS to a larger extent than PFOA [195]. Association with phospholipids in fish has also been established [196].

No instance of *metabolism* has yet been reported for PFAAs. Metabolism of FTOH-based compounds in animals or by animal tissues involves many of the pathways and metabolites identified for microbial degradation by sludge, soil or microbial cultures. There are, however, important differences: some key animal pathways involve conjugated metabolites (e.g. glucuronide-, glutathione-, sulfate-conjugates); PFCAs appear less readily, and FTUCAs more readily degraded in animals than by microbial systems; and production of PFNA, which is usually not seen in microbial systems, is observed in animals [127••]. For 6:2 FTOH, for example, metabolism in rat, mouse and human hepatocytes involves both direct and conjugate (e.g. glutathione) pathways (as for 8:2 FTOH), with PFHxA being a very minor metabolite. 5:3 FTCA and 4:3 FTCA were detected in blood plasma. An inhalation study of 8:2 FTOH in rat also found rapid uptake and systemic clearance, with similar metabolic profiles for inhalation and oral administration [197]. A pharmacokinetics study of mixtures of *n*:2 mono- or diPAPs in the rat showed decreased bioavailability with increasing *F*-chain length (diPAPs), while monoPAPs were not absorbed from the gut [85]. Hydrolysis to *n*:2 FTOH and subsequent oxidation produced PFCAs, suggesting that PAP exposure could be an indirect source of human PFCA contamination [85]. The pharmacokinetics of *F*-alkylphosphonate/phosphinate (PFPA/PFPiA) mixtures in the rat were similar to those of PFCAs, but for the fact that PFPAs (and not PFPiAs) appear to bind to blood cells, possibly because of the difference in charges [198]. Interestingly, phosphinic acids (PFPiAs) underwent P—C bond cleavage in juvenile rainbow trout, yielding phosphonic acids (PFPAs) [199]. The *F*-telomer acrylate monomer 8:2 FTAc was rapidly biodegraded in rainbow trout [200].

Biotransformation of 8:2 FTOH was demonstrated in a group of ski waxing operators exposed via inhalation to ~20,000 times higher (up to 92,000 ng/m^3 air) than standard (5 ng/m^3) levels of the substance [170]. Several metabolic intermediates, including 5:3 and 7:3 FTCAs and 6:2, 8:2 and 10:2 FTUCAs were identified in their blood.

The clearing rates of PFAAs display huge (and largely unexplained) species and gender differences [201••]. The *excretion* half-life (Table 2) of PFCAs in rats after single dose iv injection increased steadily with *F*-chain length, but irregularly for PFSAs. The pharmacokinetics of PFBS were studied in rats and monkeys, and human serum elimination was monitored in occupationally exposed workers [139]. Mean terminal serum PFBS elimination half-lives after i.v. administration were reported as ~4–4.5 h in rats (30 mg/kg$_{bw}$ dose) and ~90 h in monkeys (10 mg/kg$_{bw}$). An ~26 days half-life in humans was deduced from monitoring of six occupationally exposed subjects with an ~400 ng/mL initial mean serum PFBS concentration. The elimination half-lives of PFBA and PFOA differ by one order of magnitude for monkeys and by three orders for man (Table 2) [201••, 202•]. Angus cattle was a fast excreter for PFOA, with a 1 mg/kg$_{bw}$ dose being totally excreted (urine) within nine days [203], but not for PFOS, for which about one third of the dose (8 mg/kg$_{bw}$) was still present in the plasma after 28 days, thus becoming a potential exposure source for carnivorous humans

Table 2
Plasma or serum half-lives of major PFAAs in male (M) and female (F) mammals.
Data from [202•].

Animal		PFBA	PFHxA	PFOA	PFDA	PFBS	PFHxS	PFOS
Rat	M	9.2 h	1–1.7 h	5.6–13 days	40 days	2.1 h	29 days	38 days
	F	1.8 h	0.4–0.5 h	1.9–3.4 h	59 days	0.6 h	1.8 h	62 days
Mouse	M	13 h					28–31 days	43 days
	F	2.9 h					25–27 days	38 days
Monkey	M	40 h	5.3 h	21 days		15 h	87 days	132 days
	F	41 h	2.4 h	33 days		8 h	141 days	110 days
Human	M	72 h		2.3–3.5 years	12 years	1 month	8.5 (35)[a] years	5.4 (34)[a] years
	F	87 h			4.5 years		7.7 years	6.7 years

[a] [74].

[204]. Greatly different kinetics for PFOS and PFHxS versus PFOA and PFBA were confirmed in cows fed with contaminated feed [157]. PFOS serum half-life was 1–2 months in mice and rats, ~4 months in cynomolgus monkeys; liver/serum distribution ratios were different [205]. For PFHxS, elimination half-lives were estimated at ~2 days and 1 month for female and male rats, respectively, and ~4 months for monkeys [206]. Excretion of PFOA and PFHxS is much faster for female than for male rat (a few hours vs. ~1 month), while PFOS is excreted faster by male than by female rat (Table 2) [202•]. Serum elimination of PFNA showed half-lives of 30 versus 1.4 days for male and female rats, respectively; there was significantly higher accumulation in male mice liver than in female liver [207].

In humans, PFOA is primarily found in the liver, blood serum and kidney. A study of human autopsy tissues found, however, the highest PFAS concentrations in the lung [69]. Amazing differences in distribution were reported depending on PFAA: PFOS was prevalent in the liver and kidney, PFOA in the bone, PFHxA dominated in the liver and brain, and PFBA was most frequent and at the highest concentrations in the kidney and lung [69].

Persistence of long-*F*-chain PFAAs in humans is extremely long, with half-lives of several years. A direct human serum PFOS elimination study reported arithmetic (and geometric) mean half-lives of PFAAs in retired fluorochemical production workers (26 subjects) of 5.4 (4.8) years for PFOS, 3.8 (3.5) years for PFOA and 8.5 (7.3) years for PFHxS [208]. Similar values (4.4, 4.1 and 8.2 years for PFOS, PFOA and PFHxS, respectively) were calculated from a new-born blood spot analysis study [209]. A somewhat shorter medium serum PFOA half-life of 2.3 years was estimated by monitoring the decline (over one year only) of PFOA in citizens exposed through contaminated drinking water [107]. A similar study found a geometric PFOA mean half-life of 3.26 years [210]. An "intrinsic" elimination half-life of 2.4 years was obtained for PFOA after subtracting the effect of on-going exposure [211]. An outstandingly larger PFOA halving-time of 8.2–14.5 years was calculated from analysis of stored (1982–2009) plasma samples [72].

For PFOS, a biomonitoring study of Red Cross blood donors yielded a half-life value of 4.3 years [66••]. A larger half-life of 8.2 years was derived from the decline in PFOS serum levels observed in Swedish women [180]. Fitting a pharmacodynamics model to US NHANES data sets led to estimated PFOS elimination half-lives of 4.7 years for men and 3.7 years for women, menstruation accounting for ~30% of the difference [167]. The puzzling and unexplained out of line longer half-life of PFHxS in humans, superior to that of its higher homolog PFOS, was confirmed in a study that also noted huge differences between young women and men and older women, with mean half-lives in young females of 6.7 and 7.7 years for PFOS and PFHxS, respectively, versus 34 and 35 years for males and older females [74]. The much slower excretion rate observed for humans as compared to animals was assigned to larger renal saturable resorption efficiency [194, 212, 213]. The body half-life increase with *F*-chain length seen for PFCAs parallels that observed for fluorocarbons [2], but these half-lives are about two orders of magnitude higher, for the same *F*-chain length. Fluorocarbons benefit from an excretion route, exhalation with expired air that is clearly not available for PFAAs.

Physiologically based pharmacokinetic models have been developed that describe the pharmacokinetics of PFAAs in animals for possible extrapolation to humans in view of health risk assessment [190, 213]. Such a model, developed for monkey and extrapolated to man, allowed simulation of data collected from humans exposed to PFOA through drinking water [214]. The metabolism and pharmacokinetics of PFASs have recently been reviewed [202•].

6. Animals experience a range of adverse effects, usually at high doses

The toxicity profiles of PFOS and PFOA in vitro and in animals are slowly being refined [100, 110, 192, 215–220]. Acute toxicity of PFAAs is generally low and decreases with decreasing *F*-chain length. The liver has been identified as a specific target organ. A range of adverse effects has been observed, usually (but not always) at high doses. These effects were highly dependent on PFAS, dose, species, strain and gender.

PFAS exposure has been consistently associated with lipid and carbohydrate metabolism disorders and elevated serum cholesterol level [221–223].

Effects on the immune system include reduced lymphoid organ (thymus and spleen) weights and lymphoid cell numbers, altered T-cell populations, reduced specific antibody production, altered inflammatory responses and production of cytokines and other proteins [217••, 224, 225]. Attenuation of antigen-specific antibody responses and immunoglobulin M (IgM) antibody production was seen in mice exposed to PFOS, PFOA or Sulfluramid ($C_8F_{17}SO_2NHC_2H_5$, an insecticide) at relatively low doses, comparable to the exposure levels experienced by the most exposed human and wildlife populations (Fig. 1), suggesting a potential risk of reduced resistance to diseases [217••, 224–226].

PFAAs are recognized as endocrine perturbators [227]. Testosterone and ovarian steroid production were reduced by APFO gavage in mice [228, 229]. PFOS exposure led to deterioration of testicular signaling in mice, reducing testosterone production and sperm counts, thus impacting male fertility [230]. Exposure of human cell lines to 8:2 FTOH and 8:2 mono- and diPAPs decreased androgen and increased estrogen hormone synthesis [231]. PFOS caused apoptosis of splenocytes and thymocytes and reduction in spleen and thymus weight at high doses [232].

Developmental toxicity has raised utmost concern and contributed to long-*F*-chain PFAS regulation. The observed effects occur in animals at doses generally much lower than those causing hepatic effects. Exposure of rodents to PFOS or PFOA during pregnancy resulted in litter resorption, delayed parturition, neonatal mortality, delayed eye opening, retarded post-natal growth and liver hypertrophy [110, 229, 233–235•]. These effects depend again on PFAS, species, strain, gender and dose, but also on timing of fetal and lactational exposures. Meta-analysis of a number of animal studies confirmed that exposure to PFOA reduces fetal growth in animals [236].

In utero or early life exposure of rodents to PFOS, PFHxS or PFOA also caused developmental toxicities in adults, including pulmonary injuries [237], uterine and mammary gland development delays (or stimulation, depending on gender, strain and dose), sometimes at very low doses [26••, 91, 229, 238, 239]; glucose and lipid metabolic disorders [240]; neurobehavioral effects [241–243], all confirming that PFAAs cross the placental barrier. Substantial distribution of PFOS in lungs of neonate mice was noted that could explain the observed neonatal mortality [244], possibly by interfering with lung surfactant function. Fluorocarbons and *F*-surfactants have been shown to readily penetrate phospholipid films and bilayer membranes, and alter their phase behavior and properties [245–248]. Fluorocarbons can actually act as lung surfactant substitutes [249]. Effects on mammary gland development can differ from one strain of mice to another [235•, 238, 250]. Impaired mammary gland development in mice followed developmental exposure to PFOA in drinking water at concentrations currently found in exposed human communities [26••].

Chronic early life stage exposure of zebra fish to PFOS adversely impacted embryonic development and reproduction, sex ratio, male gonad development and larval lethality [146, 251]. PFOS concentration in eggs reduced hatching success in swallows [252]. Exposure of chicken eggs to PFOA led to cardiotoxicity [253]. Developmental toxicities of PFNA [254] and PFUnA [255] were also reported. Adult behavioral and cognitive disturbances were reported after exposure of rodent pups to PFAAs, usually at high doses [241–243]. Abnormal motor neuron development and locomotion were seen in zebrafish larvae exposed to PFAAs [256, 257]. Very little information is found about other PFASs than PFOA and PFOS, and other species, in particular wildlife.

Chronic carcinogenicity studies in rats found low incidences of benign hepatocellular, Leydig cell of the testis and pancreatic acinar cell adenomas for APFO at high doses [216, 258•], and an increased incidence of hepatocellular adenomas, but no kidney or bladder effects with PFOS (K^+) [215]. Little or no information is available for other long-*F*-chain PFASs. Numerous studies involving multiple assays found no direct mutagenic or genotoxic risk associated with PFOA, PFOS, PFBS and PFHxA [259–261].

Activation (usually reversible) of the peroxisome proliferator activated receptor α (PPARα) has been confirmed to be a prominent (but not only) *mechanism of action* for many of the prevalent toxicities observed in rodents with PFOS and PFOA [218–220, 235•, 262•–268••], including hepatomegaly and peroxisome proliferation; developmental toxicity [229, 239] immunotoxicity [225]; endocrine disruption [227]; and tumorigenicity [269]. The binding sites of PFOA, PFOS and PFHxS in the PPARα and other nuclear receptor proteins have been modeled [270]. The activation potency of PFAAs generally increases with increasing *F*-chain length. PFCAs are more potent PPARα agonists than PFSAs, and mouse PPARα is generally more responsive than human PPARα [262•, 264, 267•].

Growing evidence, including genomic data and experiments on PPARα-null (knockout) mice, indicates, however, that some biological effects of PFASs are not, or not only, dependent on PPARα activation. Other mechanisms and transcription factors can be involved, including PPARβ/∂, PPARγ, CAR (constitutive androstane receptor) and PXR (pregnane X receptor) [218, 219, 225, 263–265, 271–273••]. Some of the immune and developmental effects of PFOA have both PPARα dependent and independent mechanisms. Multiple nuclear receptors participate to the metabolic response to PFOA and PFOS exposure of both rat and human cultivated liver cells, but in markedly different ways [265]. APFO-induced liver damage and activation mechanisms were different in wild-type mice (expressing endogenous (mouse) PPARα), mice expressing human PPARα, and PPARα-null mice [274]. PFOA affected mammary gland development in both wild-type and PPARα-null mice. Gene expression profiling in wild-type and PPARα-null mice exposed to PFOS identified a variety of PPARα-independent effects [272]. Complement activation appears to be involved in hepatic injury caused by PFOA in mice [275].

PFOA and its ammonium salt APFO were eventually found by the European Chemicals Agency (ECHA) to meet the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) criteria for classification as toxic for reproduction and as specific target organ (liver) toxic, and joined PFOS on the Candidate List of Substances of Very High Concern (Section 10).

7. Human epidemiologic study results command attention

Human epidemiologic studies, although often inconclusive, inconsistent or contradictory, delivered troubling observations, requiring attentive consideration. The ubiquitous presence of long-*F*-chain PFASs in human blood, organs and breast milk, and their exceedingly long body half-lives, mean that even low exposure can eventually result in substantial body burden. Because of ubiquitous PFAS presence, there is no unexposed control population and many studies compare outcome data for high-dose sub-groups with a low-dose sub-group within the same population, a practice that can weaken dose–response correlations [276]. The dose response curves for several associations (e.g. with cholesterol and uric acid) were observed to be steepest at the lower serum levels, that is at those found in background populations (and control animals), also meaning that some effects may be difficult to determine and quantify [26••, 277].

7.1. Occupationally exposed populations

A follow-up study through 2008 of a cohort of workers exposed to PFOA (av. serum PFOA concentration 350 ng/mL; general population ~4 ng/mL) reported an increase of malignant and non-malignant renal diseases, but on limited numbers, and no exposure/response trend for diabetes or ischemic heart disease [278]. The most recent evaluation of mortality and cancer incidence in APFO production workers found no association between APFO exposure and risk of prostate and kidney cancers, diabetes and stroke [279]. The study was not powerful enough to evaluate the risk of testicular, thyroid, bladder, liver and pancreas cancers. Increases in PFOA and PFOS levels in workers involved in the demolition of a PFSA manufacturing plant showed no adverse association with lipid and hepatic clinical parameters, but for a small increase in high density lipids (HDL) with increased PFOA [280]. Little evidence for effects on lipid, hepatic or thyroid parameters was seen in highly exposed fishery employees (10,400 ng/mL serum PFOS vs. 19 ng/mL for background), but for a negative association of PFHxS with triglycerides and serum albumin, and positive associations of PFOS with triglycerides, and of PFOA with serum albumin [87]. Interestingly, some *anti*-tumor activity has been noted for APFO in human tumor (liver, colon, prostate and pancreas) xenograft mice models, leading to a Phase I safety clinical study [258•].

7.2. More exposed populations

Several non-occupational populations have been more exposed than background populations due to inadvertent drinking water pollution [26••, 80, 108]. An unprecedentedly large epidemiological study (~69,000 participants enrolled, with a geometric mean PFOA concentration of 32.9 ng/mL (general US population: 3.9 ng/mL)), the C8 Health Project (2005–2013), was set up as part of a class action settlement agreement with residents exposed to contaminated drinking water near an industrial point source of PFOA [26••, 108–111, 281, 282]. The project investigated possible links between the elevated PFOA serum levels and a large range of human diseases, usually through cross-sectional studies, and generally without establishing causality.

A modest positive association of elevated total cholesterol and low density lipids (LDL) levels with high PFOA and PFOS exposures was found in adults [222, 282], children and adolescents [281]. The dose response relationship was, however, considered as tenuous and possibly resulting from inadvertent selection bias [276]. A transcriptional

analysis that found changes in the expression of genes related to cholesterol metabolism and suggested that exposure to PFOA may promote a hypercholesterolemic environment [283] was criticized and deemed unsubstantiated [284]. Decrease of LDL cholesterol with decrease in serum PFOA after exposure to contaminated drinking water was ended, indicated a causal relation [285]. Significant positive and negative (or borderline) associations between, respectively, PFOA and PFOS serum levels and osteoarthritis, especially in women, were found in cross-sectional studies [286, 287], but not in a longitudinal study [109••].

No association was seen between elevated PFOA exposure and pregnancy outcomes, including miscarriage, stillbirth or birth defects, and lowered birth weight [288, 289], but for some suggestion of early preterm birth and possibly fetal growth restriction [290]. No association of PFOA with birth defects was found but further investigation was recommended for the brain [291]. A weak association of PFOA and PFOS for pregnancy-induced hypertension and preeclampsia was noted [289, 290, 292, 293]. A modest negative association of PFOS serum level with birth weight was reported [293]. However, mothers living near an electronic waste recycling area and exposed to twice the background PFOA level experienced higher neonatal health outcomes, including premature delivery, low birth weight and stillbirth [294].

Delayed onset of puberty (3–6 months) was observed for both girls and boys living near a chemical plant [295]. Endocrine disrupting effects of PFOA, including on steroid hormone production, have been reviewed [227]. Free serum thyroxine levels were not affected by PFOA/PFOS according to one report [296], while perturbations of thyroid function, with substantial gender differences were revealed in others [297, 298]. Augmented free thyroxine serum levels were reported in adolescents and young adults, especially males, exposed to PFNA [299]. Exposure to PFOA, PFOS and specially PFHxS has been associated with early menopause, along with a reduction of estrogen with PFOS, but not PFOA [166, 300]. No relation was found between type II diabetes incidence [301], or attention deficit and hyperactivity disorder in adolescent and serum PFOA (but possibly with PFHxS) [302]. Intriguingly, exposure to PFASs was suggested to have a neuro*protective* effects in older people, with reduced risk of cognitive limitations, especially for diabetics [303]. Weakened antibody response to vaccination against influenza in adults was associated with PFOA, but not colds or influenza [304]. Concerning cancer, two papers concluded that there was a probable link between high PFOA exposure and testicular and kidney cancers, and, at the highest exposures, with non-Hodgkin lymphoma and prostate and ovarian cancers [305, 306]. On the other hand, a strong *inverse* association between PFOS serum levels (and a more modest one for PFOA) and prevalence of colorectal cancer in a large population (~47,000, exposed through contaminated water) was seen, suggesting new strategies for preventing and treating the disease [307].

The "probable link" reports submitted by the C8 Science Panel to the Court (2011–2012) [109••, 110], about whether there was, or not, a probable link between exposure and disease concluded to probable links between exposure to PFOA and high cholesterol (but not hypertension or coronary artery disease); thyroid disease; ulcerative colitis (but not with any of the other autoimmune diseases examined, including rheumatoid arthritis, lupus, type I diabetes, Crohn's disease and multiple sclerosis); testicular and kidney cancers (but not with melanoma, thyroid, prostate, breast, liver, pancreatic, lung, brain, bladder, colorectal and other cancers); and pregnancy-induced hypertension. No "probable link" was found with liver or chronic kidney disease; osteoarthritis; Parkinson's disease; common infections, including influenza; neurodevelopmental disorders, including attention deficit and learning disabilities in children; asthma and chronic obstructive pulmonary disease; stroke; type II diabetes; and miscarriage, stillbirth or birth defects, preterm birth or low birth weight.

7.3. General population

Concerning background populations, elevated serum PFOS, PFOA, and PFNA levels have been associated positively (and PFHxS negatively) with elevated cholesterol [285, 308]. Another study found, however, a positive association with PFHxS [309]. PFOA and/or PFOS have been associated with serum uric acid [310, 311], chronic kidney disease [312], abnormal liver enzyme increases, especially in obese individuals [313], cardiovascular disease [314] and thyroid disease [315]. Different PFAAs showed different, sex and ethnicity-dependent effects on thyroid [316]. No convincing evidence was found for increased breast cancer risk in relation with serum PFAS levels [317]. Higher PFAA serum concentrations were generally not associated with increased risk of prostate cancer, except for those with hereditary prostate cancer [318]. A critical review of the epidemiologic evidence for cancer risk emphasizes that most relative risk estimates vary only from 0.5 to 2.0 (with large confidence intervals); are inconsistent and sometimes counterbalanced by negative associations; indicate no monotonic exposure response relation; and are not coherent with animal evidence [319••]. Moreover, many of the positive associations were not found in workers subjected to 1–2 orders of magnitude higher exposures. Taken together, the review concludes that the available evidence does not support a causal association between PFOA/PFOS and increased cancer risk in humans.

Effects on reproduction and development, and possibly on fertility and fecundity, are being intensively assessed. An association of higher maternal PFOA and PFOS plasma levels with longer times to pregnancy (subfecundity) was reported [320], but not confirmed [321], or was found with parous, but not nulliparous women [322]. No increased risk of preeclampsia was found among nulliparous women with background levels of various PFAAs [323]. PFOS has been associated with reduced testosterone [324]. No consistent association of PFAA exposure was seen with DNA damage in spermatozoa, apoptosis or reproductive hormones in serum, sperm motility or other semen quality parameters [325, 326]. However, in utero exposure to PFOA (but not PFOS) may affect sperm count and concentration, and reproductive hormone levels in adults [327].

Small negative effects were noted between weight at birth of female infants and PFOS (but not PFOA) level in maternal serum [328]; these girls were, however, larger at 20 months [329]. An adverse relation was reported between cord plasma PFOS content and birth outcomes, including gestational age, birth weight and head circumference, but not with PFOA, PFNA and PFUnA [179]. No probable link was seen between PFOA exposure and birth weight in an earlier review [330], or between PFOA, PFOS, PFHxS serum levels and birth weight and length of gestation [331], or even by the C8 Science Panel for a large cohort of more exposed residents [109••]. Yet, a meta-analysis including 9 studies eventually estimated that a 1 ng/mL increase in serum PFOA translated into an ~19 g reduction in birth weight and concluded that there was sufficient evidence that developmental exposure to PFOA reduces fetal growth [332]. A "Navigation Guide" review of the available human and non-human evidence concluded similarly that developmental exposure to PFOA adversely affects fetal growth in mammals [333]. Serum PFOA and PFOS levels were positively associated with hyperuricemia [311] and dyslipidemia [223] in children and adolescents, even at the low exposure levels of the US general population. Maternal PFOS and C_{13} PFCA have been related with decreased thyroid hormone levels in fetal blood [176]. Elevated exposure to PFAAs led also to reduced serum antibody levels in children subjected to routine tetanus and diphtheria vaccinations [334]. PFOA and PFOS exposures were positively associated with asthma in children [335], but positively for PFOA and negatively for PFOS with asthma in adolescents [336]. Mother reports suggested a favorable child behavior effect of PFOA exposure on boys and an adverse one among girls [337]. A tendency for obesity of female (but not male) offspring at age 20 was reported [338] that was not seen in a larger and more exposed population [339]. Later time to first menstruation was noted for women with prenatal exposure to PFOA [340]. A

longer menstrual cycle length was reported for the higher PFOA exposures [341].

A review of the current evidence for an association of PFOS exposure with health effects was inconclusive [342••]. Overt toxicity or mortality attributable to PFASs has so far not been reported in humans, even at the highest occupational levels [26••]. Epidemiological findings have recently been critically analyzed [343].

8. PFASs do not appear to behave as a class from a pharmacotoxicologic standpoint

The above summary signposts that pharmacokinetics and health effects elicited by PFASs depend widely on compound, species, gender, ethnicity, etc., are often discordant, sometimes opposite, with out of line data, often pointing to different mechanisms, for example in excretion rates (Table 2). Prediction of human health effects from animal data, or from one PFAS to another is, therefore, extremely uncertain.

A few more examples of divergent or irregular behaviors include different effects on metabolism for humans versus animals; much faster serum clearance for PFHxA than for PFBS in rats and monkeys [344]; faster elimination (~360 times) of PFHxS in female rats than in males, with serum half-lives of 2 h and 1 month, respectively [206]; slower human excretion of PFHxS than for PFOS, its higher homologue; 50 times larger excretion half-life of PFOA in humans than in monkeys (Table 2) [201••].

Multiple nuclear receptors are involved in the metabolic and other responses of human and rat hepatocytes to PFOA and PFOS exposure, but in different ways [265, 273••]. The renal organic anion transporter system that mediates renal excretion and resorption [345] may differ depending on PFCA chain length, animal species and gender [212, 346]. The immune response to PFOA and PFOS is also different: while the former reduced the number of B and T cells, the latter suppressed antigen specific antibody response independently from reduction in B and T cell numbers [224]. While neonatal mortality caused in mice is PPARα-dependent with PFOA (it is not seen in PPARα-null mice), it is PPARα-independent with PFOS (it occurs in PPARα-null mice) [347]. The mechanisms of neonatal death caused by PFOA and PFOS in mice also appear to be different [233]. PFOA induces pancreatic and testicular tumors in rats, but not PFOS [215, 216]. Both PFOA and PFOS suppress cytokine secretion by cultured human leucocytes, but through different mechanisms, dependent or independent of PPARα activation, respectively [224].

Altogether, it appears that PFOA, PFOS and other PFASs can elicit markedly different, sometimes opposite effects and use different modes of action, and that a given PFAS can cause substantially different effects in different species, genders or strains. Extrapolation/interpolation of data, for example organ distribution, from one PFAS to another, even within a homologous series, is not granted [69]. It is likely that at least part of these differences arise from the outstanding colloid and interfacial properties of PFASs.

9. Risk assessment is complicated and uncertain

Risk assessment appears particularly difficult with PFASs. A toxic equivalency factors strategy does not seem applicable because: there is increasingly strong evidence that PFAS toxicity is mediated by a plurality of receptors; the responses elicited by different PFASs are widely different and inconsistent, including within a homologous series (i.e. they do not behave as a class); for a given compound the responses (and modes of action) depend widely on species and even strain and dose; additivity of effects had not been established and is improbable in view of the above points; and the available toxicological database is limited to very few compounds, mainly PFOA and PFOS [273••]. Dosimetric anchoring approaches developed for comparing specific toxicity studies appear foiled for lack of appropriate information, in particular about short-*F*-chain and other alternative PFASs [348]. The uncertainty factors used to account for inter and intraspecies and other differences reach 2–3 orders of magnitude [89••]. The long-term effects on environment and human health of PFASs, long or short, remain uncertain. Economic and societal pressures are important. In view of the considerable amount of uncertainty, the precautionary principle should likely prevail.

PFAS toxicity data for humans are scarce, fragmentary and often inconclusive (Section 7). Risk assessment needs therefore to rely weightily on animal data, mostly collected for PFOS and PFOA. These data show considerable, often inconsistent variability (Sections 6 and 8), raising the question of the relevance of animal models and data for human risk assessment [201••, 206, 349, 350]. The PFAS, gender, species, etc. variations, complex pharmacodynamics behavior and toxicity mechanisms are presently not fully understood or predictable [201••, 351••, 352••]. Some animal data are definitely inappropriate. This is the case, in particular, for those collected on female rat for which PFOA excretion is so fast (a few hours) that a steady state is not reached through daily dosing, thus reducing fetal exposure and invalidating assessment of potential developmental effects in humans [26••].

Concerning humans, gender differences in responses are also substantial with generally higher PFAS levels in man than women [58••, 63••, 67, 70, 72, 73, 283, 300]. Ethnicity, life-style and dietary habits effects were also noted [63••, 77].

Many of the major toxic effects observed in rodents, have been traced to PPARα activation. However, PPARα expression is much less pronounced in human than in rodents [268••, 269, 353, 354]. Liver, pancreas and testis cancer inducement by PFOA in rodents does not appear to be relevant to cancer inducement in humans [269]. The combined PPAR and CAR/PXR activation mechanism assigned to hepatomegaly in rats after chronic exposure to APFO was considered unlikely to cause a human hepatocarcinogenic hazard [263].

Little is known yet about possible combined mixture effects with other chemicals, drugs and pollutants. Binary combinations of PFOA with PFNA, PFHxA, PFOS or PFHxS behaved additively in terms of PPARα activation in vitro at concentrations relevant to current exposures [355]. Mixtures of PFOA, PFNA, PFHxS and PFOS in ratios based on serum levels in NHANES subjects showed a less than additive effect on PPARα activation, reflecting possible antagonistic interactions [356]. Exposure of zebrafish embryos to mixtures of PFOA and PFOS revealed a complex interactive toxicity pattern, changing from additive to synergistic, then to antagonistic, and eventually to synergistic again with increasing PFOS molar ratio [357]. Yet, a risk assessment study from combined exposure to multiple PFASs, concluded that there was no significant cause for concern for humans, except for high fish consumers and ski waxers [358].

Altogether, it appears that PFASs do not behave as a class, that their biological behavior is highly dependent on species, gender, etc. and unpredictable, and that, while most data focus on PFOA and PFOS, the biological effects of the other PFASs, in particular the more recently used alternatives to long-*F*-chain products, remain largely unknown. Relevance of animal data to human risk assessment is still being debated. A recent PPARα case study Panel's opinion was that the rodent mode of action is not relevant or unlikely to be relevant to humans [268••]. Concerning PFASs other than PFOA and PFOS, risk assessment suffers dearly from lack of information about identity, sources, tonnages emitted, degradation products and metabolites.

10. Regulation and voluntary actions have been decided and implemented

Once the environmental persistence and bioaccumulation potential of long-*F*-chain PFASs had been recognized, some action had to be taken (Fig. 3). In 2000, the 3M Company, under the guidance of the US Environmental Protection Agency (USEPA), started phasing out its production of PFOS, PFOA and related compounds. The USEPA then established a Stewardship Program involving eight major chemical companies in Western Europe, the United States

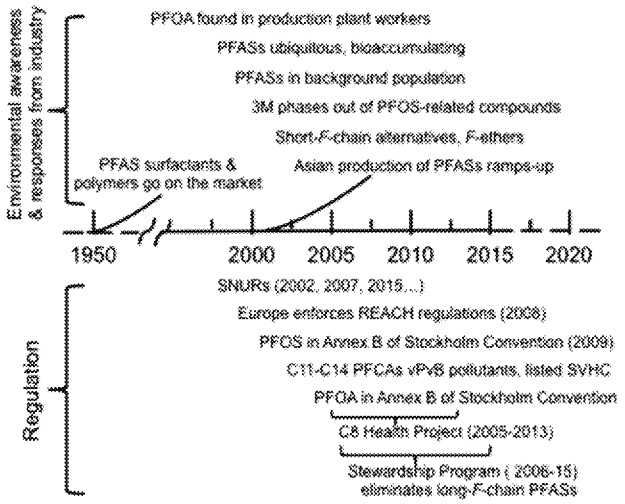

Fig. 3. Brief history of PFAS production and regulation.

and Japan that 1) aimed at a 95% reduction by 2010 of facility emissions of PFOA precursor chemicals that can break down to PFOA and related higher homologues, and of content levels of these chemicals in final products; and 2) committed to working toward the elimination of these chemicals from emissions and products by 2015 [92]. The 2014 progress reports are now available [359]. Another voluntary action led to virtual elimination of PFOS use in semi-conductor production [360].

Since 2009, POSF, PFOS, their salts, higher homologues and related chemicals are listed in Annex B of the Stockholm Convention on Persistent Organic Pollutants as very persistent, very bioaccumulative (vPvB) and toxic, and their production and use are strictly restricted [361–363••]. The Convention and other regulations recognize, however, production and use for acceptable purposes, such as for mist-suppression during metal plating (but only in closed-loop systems), control of leaf-cutting ants, aviation hydraulic fluids, photo-imaging, photo-resist and anti-reflective coatings, medical devices, etching agents for semiconductors, fire-fighting agents [2••, 3••, 362]. On the other hand, the pesticide Sulfluramid is to be phased out by 2016. It should be noted that PHxSF derivatives are not acceptable as they are potential precursors of long body half-life compounds [3••].

In 2012, the very long *F*-chain C_{11}–C_{14} PFCAs have been categorized as vPvB potentially harmful pollutants and recorded in the Candidate List of Substances of Very High Concern (SVHC) for Authorization under the REACH regulation [110]. PFOA and its ammonium salt (APFO) clearly fulfill the persistent, bioaccumulative and toxic (PBT) substance criteria [364]. They were identified as such by the EU and joined the SVHC list in 2013 as toxic for reproduction [110]. In 2014, an International Agency for Research on Cancer working group also classified PFOA as possibly carcinogenic in humans [365]. *F*-Polymers are no longer exempted from pre-manufacture (or importation) notification in the US [366]. A proposed 2015 US Significant New Use Rule (SNUR) ensures that PFASs that have been phased out do not re-enter the marketplace without review [367].

Agencies in charge of public health protection establish recommended values for provisional pTDIs. Therefore, an animal no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-level (LOAEL) for a selected critical endpoint (e.g. liver weight increase, triiodothyronine hormone production decrease) is often used for human risk assessment. This NOAEL or LOAEL provides a point of departure dose or exposure level to which various uncertainty factors (2–3 orders of magnitude) are applied (so as to account for intra- and interspecies variability, experimental duration, strength of database, etc.) in order to derive a TDI, predicted no-effect value (PNEC), drinking water advisory value or other reference values (Fig. 1).

In 2008, the EFSA proposed pTDI values of 150 ng/kg_{bw}/day for PFOS and 1500 ng/kg_{bw}/day for PFOA on the basis of animal studies [45]. The TDI for PFOS is generally above the indicative figure estimated by EFSA for human exposure, but could be exceeded for the highest exposed populations (as by high fish consumption, or occupational exposure) (Fig. 1) [87, 89••]. For PFOA this value is well above the indicative value for average human exposure, although lower pTDI may be desirable for children.

Establishing guidelines for drinking water is also critical in terms of public health protection. Maximum tolerable values differ somewhat depending on country and agency and range from 0.04 to 0.5 ng/mL for PFOA and 0.2–0.3 ng/mL for PFOS [81, 89••]. The USEPA, for example, has set provisional health advisory values of 0.2 and 0.4 ng/mL for PFOS and PFOA, respectively, in drinking water [92]. Preliminary reference values that should trigger a search for sources of contamination were recommended in Germany for PFOS in blood plasma to be 10, 15 and 25 ng/mL for children, adult females and adult males, respectively, and 10 ng/mL for PFOA (all groups). In the US, six PFASs have been listed in the proposed third Unregulated Contaminant Monitoring Rule (2012–2016) for drinking water safety, with minimum reporting levels (ng/mL) set at: PFOS (0.04), PFHxS (0.03), PFBS (0.09), PFNA (0.02), PFOA (0.02), and PFHpA (0.01) [368]. Concerning the shorter *F*-chain acids, the provisional health-related indication values for drinking water to be considered safe for life-long exposure were the following (ng/mL): for PFBA: 7; PFHxA: 1; PFHpA: 0.3; PFBS: 3; and PFHxS: 0.3 [81]. Water quality criteria are also being set in China [369•].

11. The need for and compliance with regulation is not global

One serious glitch in the regulation of production and use of long-*F*-chain PFASs is that companies that did not adhere to the USEPA Stewardship Program immediately started or increased production of these PFASs in order to meet increasing market demands and development needs. This resulted in a prompt geographical shift of production areas, mainly to continental Asia. A clear-cut distinction was made between two groups of countries: those committed to the Stewardship Program (North America, Western Europe and Japan) and those that are not (mainly China, India, Poland and Russia) [4••]. POSF-based production and uses appear to have virtually disappeared from the western countries where they have been replaced by alternative shorter-*F*-chain products or long-*F*-chain ether derivatives. Correlatively, large-scale production started in Asia to fulfill extensive needs for carpet, textile and leather treatment and other uses (Fig. 4, Section 13) [4••, 370].

While regulations are indispensable for pollution control and rational management of PFAS risk, they also have limitations and downsides, including a negative economic impact on growth of development. Enforcement of regulations is further complicated by the multiplication of proprietary variants and the fractionation of use among many, often undisclosed PFASs or mixtures thereof. This practice, by reducing tonnages used in a given location below analytical "visibility" or below certain regulatory thresholds (e.g. the 100 tons limit that requires data on bioaccumulation for REACH authorization [371]), renders global monitoring, regulation and control of implementation virtually impossible. This is the case for the *F*-polyethers that have replaced PFOA and PFNA in *F*-polymer manufacture [352••, 372] (Point/Section 13). Multiplication of components in a technical product [16–18] also complicates the regulators' task. For lack of information, some PFASs have remained unnoticed while already in use for 30 years [373]. Certain compounds, by formally changing categories (e.g. from polyether to polymer [352••]) may also elude regulation. Some rules do not apply to imported finished goods. While direct emissions of regulated substances decrease, emissions of these substances through production and degradation of precursors continue. Finally, the counter risks posed by any PFAS alternative need also to be evaluated and taken into consideration [89••].

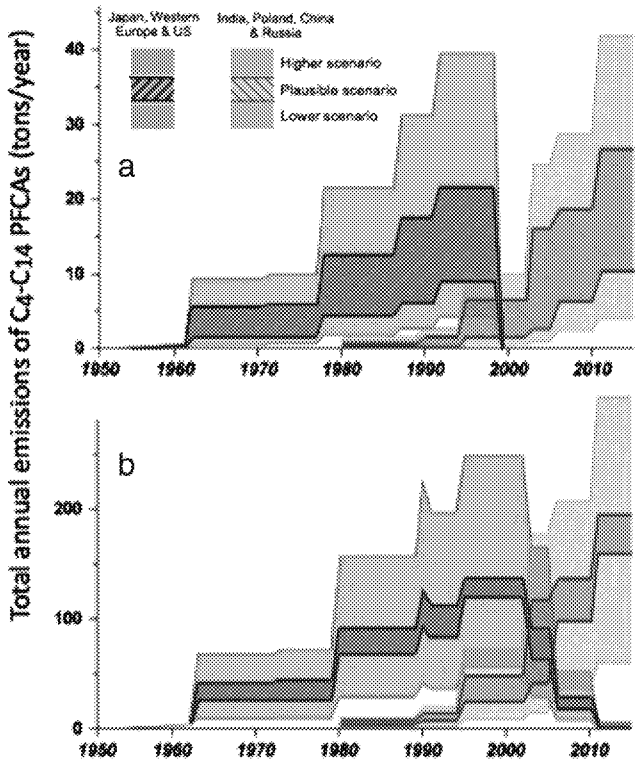

Fig. 4. Estimated annual releases of PFCAs from a) PFOA production sites and b) fluoropolymer production sites in the United States, Western Europe and Japan (blue), as well as in China, Russia, Poland and India (orange). The colored areas are the estimated ranges of annual emissions based on the full ranges of the APFO/NaPFO use rates from patents. The areas shaded in dark are the estimated ranges of annual releases based on an APFO/NaPFO use rate of 0.3 wt.% of relevant fluoropolymers produced (plausible scenario).
Adapted from [4].

12. Trends in production and exposure are diverse and sometimes divergent

The two groups of countries identified as complying, or not, with the Stewardship Program to reduce long-*F*-chain PFAS production and use, have started PFAS production at two distinct time points (Fig. 3), causing a geographical shift in long-*F*-chain PFAS production and emission sources (Fig. 4) [4••]. In China, about 10,000 tons of PFOS-based compounds have been used in 2009, mostly for textile treatment [374]. PTFE production and PFOA use have increased ten-fold between 1999 and 2012 [4]. Globally, the local PFCA release decreases of all long-chain PFASs taken together appear to be outweighed by increases in other areas, causing overall emissions to increase again (Fig. 4). Auspiciously, regulations, freshwater protection, recycling of PFOA and use of alternative agents, have begun in China [4••, 44••, 369•]. There is, however, little reason to believe in radical reduction in PFAS exposure in the near future. Indeed, the unique and outstanding properties of PFASs, and the societal and commercial benefits they generate, spur augmenting demands, especially from developing countries. Concurrently, the considerable amounts of precursors of long-*F*-chain PFAAs that are stored in our carpet, soil, snow and ocean reservoirs are being slowly released.

Definite decreasing exposure trends have been recorded for some, but not all, of the now regulated historical long-*F*-chain PFASs. Developing countries experience increased long-*F*-chain PFAS pollution in their most developed areas, especially in certain industrial cities and downstream and coastal waters [40, 41, 44••, 169, 369•, 375]. Increased amounts of PFASs, predominantly PFOS and long-*F*-chain PFCAs, are reported in water, sediments, soil and biota, particularly in the higher trophic level organisms, potentially causing adverse effects to wildlife.

The relative contributions of individual PFASs to global emissions have also changed over time, although PFOS is still the dominant fluorinated pollutant detected essentially everywhere. After 2002, long-*F*-chain PFAAs from direct sources have become less relevant, while emissions related to degradation of hundreds of long-*F*-chain precursors, including polymers with fluorinated side-chains that were produced in very large amounts, have become significant [4, 85]. Short-*F*-chain products production and emissions have increased markedly [376]. PFBS is now being detected ubiquitously. 6:2 FTOH has become more abundant than 8:2 and 10:2 FTOH [11]. The levels of FOSEs and FOSAs have decreased over the 2006–2011 period but emissions related to 8:2 and 10:2 FTOHs, after a slight decrease, have increased again [42]. The global *F*-polymer market is growing steadily at a 5–6% annual rate. PFAS production, emission trends and population exposures have recently been analyzed in detail [76••].

Another trend that has already been alluded to is the increase of the number and variety of PFASs detected (often incidentally) in the environment. Information about these more numerous, less conspicuous, largely unpublicized PFASs, their identity, production volumes, performances, uses, degradation products and metabolites, and potential health effects are at best rudimentary.

There is a recent trend for PFOS levels to decline in the arctic in some species and locations, while they still augment steadily in others (including in polar bears on their "pristine" ice fields for which PFOS and long PFAAs serum levels can exceed those found in the more exposed human populations!) [37•, 52•]. While PFOS is marking time, long-*F*-chain PFCAs continue to increase steadily in sea mammals [377] and polar sea bird eggs [54]. On the other hand, PFOS and PFHxS concentrations in farmed fish and eggs have decreased sharply over the 1999–2010 period in Sweden, demonstrating a rapid response to reductions in emissions [378]. Altogether, temporal trends in contamination levels depend on PFAS, animal species, location, etc. leading to somewhat inconsistent reports. Despite decreasing concentrations of many PFAAs in South Korean water, concentration in aquatic organisms did not decrease over time (2008–2010), due to continuous bioaccumulation [141].

Downward trends of PFOS and PFOA concentrations measured in human blood and milk also indicate that, where enforced, regulations are efficacious. These trends are, however, not uniform (Fig. 2). Data from the US NHANES over the 1999–2008 period show a significant decrease of PFOS in human serum, while PFOA, after a decrease, remained essentially constant between 2003 and 2008, but seems to decrease again; PFNA continued increasing (possibly in relation with 8:2 telomer degradation); PFHxS decreased until 2006, then increased again [63••, 379]. Over the 2000–2010 period, PFAA levels in the plasma of adult American Red Cross blood donors featured a decline in geometric mean concentrations of 76% for PFOS, 40% for PFHxS and 48% for PFOA [66••]. Serum concentrations of PFOA, PFOS and FOSA in Swedish women during pregnancy and nursing have decreased (2000–2010), while those of both longer (PFNA, PFDA) and shorter (PFBS, PFHxS) compounds increased markedly [180]. PFOS decreased radically (from 20 to 24 ng/mL to 4 ng/mL) in human plasma in Germany between 2001 and 2010, while PFOA only started decreasing around 2008 [70]. Other studies found decreased serum levels during the 2000–2009 period for PFOA, PFOS and several sulfonamidoacetates in urban German populations, but not for PFHxS, while PFNA, PFDA and PFUnA levels continued increasing [72, 73]. Numerous PAPs were also detected and showed no significant decrease in concentration. Serum PFOA levels increased in Seoul and decreased in Japan in highly exposed areas (Osaka), but not in low exposed areas [380]. PFOA and PFOS serum concentrations declined markedly in Australia over the 2002–2011 period [78•]. The serum concentrations of nine PFAAs and three *F*-sulfonamides in the US population have been compiled from NHANES biomonitoring data [112].

Human milk time trends for PFOS, PFHxS and PFOA showed a clear decrease, from ~230, ~25 and ~130 pg/mL to 75, 14 and 74 pg/mL, respectively, between 2000 and 2008 in Stockholm [95]. Decrease of PFOS in milk was also reported in Italy [93].

13. There are, as yet, no genuinely satisfactory alternatives to long-*F*-chain PFASs

The FluoroCouncil [381], a global organization representing the Western World's leading fluoro-technology companies agreed to the following transitional changes in production of *F*-surfactants: from ≥ C_6 to C_4-based sulfonates; from ≥ C_8 to C_6 *F*-telomers; and from C_8 and C_9 *F*-carboxylate polymerization aids (PFOA/PFNA salts) to poly-*F*-ether-based acids (Table 1). The shift to shorter-*F*-chain compounds is essentially grounded on the finding that they are less bioaccumulable and benefit from shorter body half-lives. The alternative polymerization aids derive formally from the formerly used ones by the introduction of ether functions or other "weak points" within the long-*F*-chain that were deemed to facilitate degradation. But the current alternative PFASs, for as much as they have been identified, hardly provide satisfactory solutions to the technical and environmental problems of long-*F*-chain PFASs.

13.1. To which extent are short-F-chain PFASs effective?

Current regulation considers that PFCAs with *F*-chains of less than 7 carbons and PFSAs of less than 6 are not bioaccumulative and have little biomagnification potential [3]. Shorter PFAAs also appear much less toxic, although the consequences of higher vapor pressure, water solubility, mobility, different partition behavior, etc. are not yet fully evaluated. Claims that their performances are close to those of their longer-*F*-chain homologues are somewhat perplexing.

The manufacturing principles that underlie the production of the shorter-*F*-chain product lines are essentially the same as those used for their now banished longer-*F*-chain homologues [1••, 2••]. Although shorter on the average, most products still consist of highly complex, largely unpublicized mixtures with dozens of components that sometimes still include long-*F*-chain compounds [17, 372]. Short-*F*-chain PFCAs and PFSAs have essentially the same thermal stability and chemical inertness as their longer-*F*-chain homologs. They are as refractory to degradation and metabolism, and as persistent in the environment.

Performances in terms of surface tension lowering efficiency, film-forming ability and film stability diminish drastically when *F*-chain length diminishes and water solubility increases [2••]. While 8- or 10-carbon-long linear *F*-chain amphiphiles (e.g. carboxylic acid- and phospholipid-based *F*-surfactants or even *FnHm* diblocks (Table 1)) readily form sturdy insoluble monolayers on water with high collapse pressures, their 4- or 6-carbon homologues generally fail to form stable molecular films [382]. The self-assembling capacity, packing organization, formation of ordered liquid condensed phases, and viscoelastic properties of interfacial surfactant films are also extremely sensitive to *F*-chain length [383–387]. 6:2 *F*-telomer sulfonates were deemed less effective than PFOS for hard-metal plating by the United Nations Environment Programme (UNEP), which encourages research for better performing substitutes [388]. Lesser efficiency means that larger amounts of surfactant need to be used. Yet, many reports and communications suggest that the commercial C_4 and C_6-based surfactants do provide the performances required for most standard uses. Reconciling this claim with the physicochemical basics of *F*-surfactants is problematic. The notion that the short-*F*-chain PFASs are generally effectual in spite of lesser physical performance logically raises the question whether decades of use and release to the environment of long-*F*-chain PFASs were befitting.

Some of the environmentally relevant physical properties of the short-*F*-chain PFASs (e.g. higher water solubilities, vapor pressures, weaker adsorption on and easier elution from particles) result in higher mobility [376, 389]. Faster adsorption/desorption at interfaces can be beneficial, for example in certain printing and coating processes, but it also accelerates leaching occurrences and environmental dissemination and contamination. Shorter-*F*-chain PFASs are transported faster and at greater distance from source, and riverbank sediment depuration may be inefficient [389].

Biological transfers are also facilitated, for example from maternal to cord serum in humans [176]. The rate of uptake of PFAAs by plants (e.g. maize, lettuce) increases with decreasing *F*-chain length. Greater amounts are transferred from soil to the shoot or leaves, meaning greater human exposure through foodstuffs [390–393]. Shoot and fruit crops may have 1 to 3 orders of magnitude more PFBA than PFOA if the two are present equally in the soil [392].

Concomitant with increased production, short-*F*-chain substances, primary PFBS, PFBA and PFHxA, are now increasingly often detected in the environment [5•, 55, 68, 141, 394]. PFBS and PFBA have become dominant contaminants of river waters [43, 395], lakes [87], and significant in the northern oceans and arctic snow [8], polar ice [396], drinking water [5•, 26••, 81] and humans [69, 180]. PFHxA levels were substantial in drinking water downstream of a fluoropolymer manufacturing plant [25]. Alpine snow has undergone a change from PFOA- to PFBS-dominated PFSA composition [394]. PFBS, PFBA, PFHxA were among the numerous and abundant PFSAs identified near military bases [16]. PFBS- and 6:2 FTOH-based chemicals are subject to atmospheric degradation processes similar to those found for their longer-*F*-chain homologues [36••]. The degradation of the short-*F*-chain polyfluorinated amide $C_3F_7C(O)NHC_2H_5$ eventually lead to PFCAs, including PFBA [397].

Although the shorter-*F*-chain PFASs have now been in use for a number of years, our understanding of their health and environment impact is still unsatisfactory, and their risk assessment still uncertain [351••, 352••].

13.2. To which extent are F-alkyl ether PFASs degradable?

The manufacture of polymers with polyfluorinated backbones requires the high level of performance that is presently only attainable with long-*F*-chain processing aids. In order to circumvent the environmental issues of the historic PFOA/PFNA-type processing aids, ether oxygens or other "weak points" were introduced in the *F*-chain that would ensure degradability while the acid function and total number of fluorinated carbons remained essentially the same. However, the claimed degradability advantage of these new long-*F*-chain ethers (PFECAs and PFESAs, Table 1) in environmental conditions is not yet clearly established, and their toxicity profile and that of their degradation products remain uncertain. The still limited public information available about their production, use, environmental exposure, persistence and exposure of biota and humans has recently been discussed [352••, 372].

There is actually little experimental evidence to support the expectation that PFECAs and PFESAs would be rapidly degraded in the environment. The ether oxygens are sterically sheltered and electron-depleted by the bordering electron-withdrawing *F*-chains, and thus inactivated. An in silico study estimated the basic properties, degradation half-lives and transfer efficiency of PFECAs and PFESAs, and concluded that their behavior, including their persistence and mobility in the environment, should not be significantly different from those of the substances they replace [398]. Their thermal stability, resistance to photodecomposition, hydrolysis and reaction with OH radicals under environmentally relevant conditions appear indeed to be similar to those of regular *F*-alkyl chain PFAAs [36••, 352••, 372]. ADONA (Table 1) for example, has been described as stable, not readily biodegradable and non-reactive, and a decomposition temperature of 125–175 °C was reported [250] that is similar to that of NH_4^+ PFOA, 167 °C [399]. Decomposition of PFECAs required combining persulfate $S_2O_8^{2-}$ oxidation and ultrasonic irradiation [400]. There is little or no evidence for lesser bioaccumulation potential for PFECAs/PFESAs as compared to their PFCA/PFSA analogues, or indication of atmospheric degradation, or different biological handling

and toxicity mechanisms [352••]. No metabolism has been reported. There is no evidence that their eventual (largely unknown) degradation products are innocuous. Releases of ADONA and GenX (Table 1) have been identified nearby factories [372]. The toxicity profile of ADONA was deemed superior to that of PFOA, but the two products were evaluated under different conditions [250]. GenX was actually suggested to be classified as having, like PFOA, specific target organ toxicity (STOT) by its producer [352••]. F-53B (Table 1) was found as persistent, similarly toxic in zebra fish and likely as bioaccumulative as PFOS [373]. Human data on ether acids are essentially inexistent. A (surprisingly short) human serum elimination half-life of 559 ± 254 h (3 male workers) has been suggested for ADONA [401].

Assessment of the bioaccumulation potential and toxicity of ADONA and other ether-type alternatives was not considered possible for lack of relevant data [110], but there seems to be little reason why long-*F*-chain PFECAs/PFESAs should not be classified in the same hazard category as PFOA/PFOS under REACH and other regulations. What has been described as a possible "lock-in" situation may have been created, in which the chemical banished from the market is replaced by other chemicals of essentially the same group with only minor structural changes, without solving the basic problem raised by the former product [372, 402•]. We simply know less about them.

14. There is a need for genuine breakthrough products and technologies

Matching the full spectrum of outstanding performances obtainable with long-*F*-chain products without fluorine is not a trivial challenge. Long-*F*-chain surfactants and polymers can indeed *simultaneously* provide utmost hydrophobicity and lipophobicity, extreme surface activity (effectiveness and efficiency), phase-separation and compartmentation ability, highly stable and thin self-assembled condensed film-forming capacity, tunable wetting properties, ultimate thermal stability and chemical inertness, excellent sun light resistance, water refractivity matching, and all this at reasonable cost, generating innumerable industrial and every-day uses [2••, 403–406]. The present (hopefully temporary) alternatives are merely variants of established commercial products. More creative responses and radical, disruptive technologies are required. We need to conceive, synthesize and assess conceptually new, cost-effective compounds or systems whose performances would approach those of long-*F*-chain PFASs, yet with shorter, possibly multiple *F*-chains, lesser amounts of fluorine, or none. Recourse to several very short-*F*-chains (rather than one long one) or terminal CF_3 groups may suffice for certain uses and recognition purposes [407], in particular when extreme thermal stability and surface activity and potent self-assembly potential are not simultaneously required. This strategy may be effective with polymers, for which fluorinated film formation and stability do not depend on hydrophobic self-assembly. Assembling in a molecule fluorinated patches made of a set of contiguous CF_3-, CF_3O- or C_2F_5 units, resulting in a sort of surface fluorination at the molecular level, may suffice to express potent "hyper" hydrophobic and lipophobic characters for certain uses [383]. Could bioinspired systems (think about the lotus effect) help conceive *F*-like performances without fluorine? But then, what about resistance to harsh conditions? Ideally, one should find or generate and breed microorganisms ("bugs") that would feed on *F*-chains and release chocolate. Alas, this covetable approach has, to our knowledge, not yet materialized.

The presently explored avenues include use of still shorter or branched or multiple short *F*-chains, and introduction of weak points to facilitate chain degradation, and combinations of such approaches. The surface properties of an amphiphile bearing two C_4F_9 chains were, for example, found comparable to those of an analog bearing one C_8F_{17} chain [408]. One or two CF_3 groups located at the end of a hydrophobic chain (e.g. $CF_3O(CH_2)_nSO_3Na$, $(CF_3)_2N(CH_2)_nSO_3Na$, $CF_3(C_6H_4)O(CH_2)_nSO_3Na$; $n = 8–12$) can already produce a significant gain in surface activity versus standard hydrocarbon surfactants [409]. Surfactants with two or three short C_2F_5 or C_3F_7 chains fitted on carbohydrates or PEG polar heads have been synthesized [410]. A surfactant of undisclosed structure went commercial that, with three C_2F_5 groups, was reported to provide a surface tension of 20 mN m^{-1} at a concentration of 0.1 wt.% [411].

Biomonitoring of PFAAs in human urine indicated that major branched PFOA and PFOS isomers may be excreted faster than the linear one (although one PFOS isomer had an estimated 90-year half-life) [74]. On the other hand, branched isomers appear to cross the placenta more efficiently than linear ones [412]. *F*-chain branching tends also to decrease *F*-surfactant efficiency and aptitude to organize in compact films on surfaces. Even if the gains in terms of bioaccumulation, excretion rate and toxicity were significant, and functional efficacy comparable, cost-effective large-scale separation of specific PFAS isomers does not seem realistic.

The creed that inserting "weak" points into the chain's backbone may facilitate *F*-chain degradation has been around for a while. If effective, this approach means that one would forsake one of the major assets of *F*-chemicals, their resistance to harsh conditions. Introduction of ether oxygens, —CH_2-, —CHF- and other groups, or alternating CF_2 and CH_2 groups in *F*-chains has been achieved, but degradability in environmental conditions has generally not been established. Several sulfonates (e.g. $C_3F_7OCF_2CF_2CH_2CH_2SO_3H$, $C_6F_{13}CH_2CF_2CH_2CH_2SO_3H$), sulfamido betaine and sulfamido amine oxide surfactants derived from $C_3F_7OCF_2CF_2CH_2CH_2SO_2Cl$ and $C_4F_9(CH_2CF_2)_{(1\text{ or }2)}CH_2CH_2SO_2Cl$ have been synthesized [413, 414], as well as oligo(vinylidene fluoride) telomers $C_nF_{2n+1}(CH_2CF_2)_xCH_2COOH$ ($n = 2, 4$; $x = 2$) [415]. Various surfactants that combine an *F*-isopropyl terminal group with pending CF_3 groups located on alternate carbons along the hydrophobic backbone had surface tensions comparable to that of PFOA [416]. Sequential block copolymerization of vinylidene fluoride, trifluoropropene and vinyl acetate led to surfactants that combine a terminal C_6F_{13} chain, isolated CF_2 groups in the backbone and pending CF_3 groups [417]. Their environmental behavior, degradability, pharmaco- and toxicodynamics remain to be investigated. Identified alternatives to PFOS-related PFASs (with not only short-*F*-chain homologues) have been listed [3, 363••, 418].

Other approaches may use (innocuous enough) particles, such as silica, laponite clay or polystyrene latex, as dispersion (emulsions, multiple emulsions, foams, etc.) stabilizing agents [419, 420]. For food products, polysaccharides (starch, cellulose) or protein-based particles (casein) or protein/polysaccharide associations are being developed [421]. All these approaches require evaluation of any counter-risk posed by particle use.

15. More considerate, restrained use appears reasonable

Among the unavoidable "cleanup" tasks foisted by both legacy and novel PFAS pollutants one can cite, detection, monitoring and reduction of point sources; development of technologies for removal of PFASs from drinking waters; establishment of effective wastewater cleaning procedures, and realistic ways of decomposing PFAAs.

Regulation of PFAS production and use need obviously to be extended and enforced globally. However, concerns about environmental impact versus economic development, need for regulation and compliance with regulations are obviously not being shared evenly by all and every country and company around the world. Global agreements on reduction/monitoring/control of production/emission/exposure need to be shaped that are acceptable by the largest possible number of countries. There are auspicious indications that reduction of emissions and use of alternatives to long-*F*-chain PFASs are now considered in the countries that are producing them, but no timelines appear to have been set [4••]. Any regulation or ban on PFASs will likely impact developing countries more severely than developed countries who are better equipped for devising substitute strategies [4••].

While waiting for (exclusively) fluorophagic bugs to cleanup the mess, more responsible use of PFASs would appear wise. Responsible

conduct commands that long-*F*-chain compounds use be restricted to applications for which societal benefit/risk ratio is clearly proven, such as those related to safety, health, energy and high technology devices and close-circuit uses. All uses do obviously not simultaneously require the full set of extreme properties only provided by long-*F*-chain compounds. Optimization of fluorine content/performance/need for performance has to be considered systematically. Liberal use of high tonnages of the shorter-*F*-chain compounds should not be granted. High tonnage convenience applications should preferably be left to non-fluorinated products (provided they are less persistent and safe). Risk versus benefit to society (e.g. safety, energy and raw material savings) needs to be evaluated for each high tonnage application. The counter risk associated with any alternative solution needs also to be taken into consideration. These are not easy tasks.

16. Knowledge and information gaps impede effective PFAS risk management

Uncertainties about properties, pharmacokinetics and toxicity, environmental fate, and risk remain considerable. Knowledge gaps about PFASs are many and seem growing as marketed products grow in number and complexity. The eventual fate of PFAAs, long or short, remains uncertain. They are likely to cycle through biota along with other POPs. Effects on endocrine and immune systems, developmental issues are still poorly understood, even for the most investigated PFASs. Many critical papers close with increasingly long TO DO lists.

Other than for a handful of PFAAs, independent public information about the identity, chemistry, production, physicochemical properties, technical performances, environmental behavior, exposure, degradability, pharmacokinetics and toxicity is quite limited. This concerns, in particular, the multiple new low tonnage short-*F*-chain variants and long-*F*-chain polyether-type processing alternatives and new formulations brought on the market. Restricted sharing of information, especially from industry, is a serious obstacle to risk/benefit assessment and rational PFAS management. Lack of such information can legitimately raises the question whether a new product has been properly tested prior to marketing, and carries a liability [352••].

17. A multidisciplinary challenge is on our hands

Future efforts aimed at advancing environmental PFAS management issues need to be eminently multidisciplinary and should concern all the actors of the global scientific, industrial, regulatory and user communities, worldwide [1••, 351••, 372].

The challenge for Colloid and Interface chemists is to help fill in knowledge gaps about the physicochemical behavior of PFASs, investigate the likely role of their specific "super" hydrophobic, segregating, self-assembling and interfacial comportment in their apparently inconsistent pharmacokinetic and toxicity behaviors, and contribute to providing creative answers and answerable solutions to growing global demand for high-performance materials, while exercising responsible ecological and societal awareness.

Risk needs to be maintained at an acceptable level, compatible with technological innovation, economic growth, and preservation of health and environment. The necessary and urgent research efforts require improved coordination, sharing of expertise and information. Our challenge is to manage (or replace) PFASs so as to contain/reduce pollution and health risks, without losing the technical and societal benefits of their use and, in particular, without penalizing the developing countries.

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